APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 11
Species: human

Minimal Risk Level: 2 [ ] mg/kg/day [X] ppm

Reference: Young JD, Braun WH, Rampy LW. 1977. Pharmacokinetics of 1,4-dioxane in humans. J Toxicol Environ Health 3:507-520.

Experimental design: The acute-duration inhalation MRL is based on a LOAEL of 50 ppm for eye irritation in humans in a study with volunteers. In that study, the effects of 50 ppm 1,4-dioxane vapors were evaluated in four healthy male volunteers. Prior to the study, the subjects provided a complete history and underwent tests including chest x-ray, EKG, respiratory function tests, a conventional battery of 12 blood chemistry tests plus triglyceride and creatinine determinations, and complete hematological and urine analyses. Except for the chest x-ray, the tests were repeated 24 hours and 2 weeks after the exposure. The exposure was carried out in a 26.7 m^3 chamber under dynamic airflow conditions.

Effects noted in study and corresponding doses: The tests conducted 24 hours and 2 weeks after exposure did not reveal any exposure-related abnormalities. Eye irritation was a frequent and the only complaint throughout the exposure, but no data were provided in the study. Tolerance to the odor of 1,4-dioxane occurred during exposure. Two of the subjects could not perceive the odor after 4 and 5 hours in the chamber. The LOAEL of 50 ppm was divided by an uncertainty factor of 30 (3 for a minimal LOAEL and 10 to protect sensitive populations) to derive the MRL. Because the effects observed were local irritation effects, they were not time-dependent, an adjustment to 24-hour exposure was not necessary.

Dose and end point used for MRL derivation: 50 ppm; LOAEL for eye irritation in humans.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[ ] for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? NA.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information which lend support to this MRL: Other studies with volunteers support the finding of Young et al. (1977). For example, Silverman et al. (1946) exposed

12 subject to various concentrations of 1,4-dioxane for only 15 minutes and determined a NOAEL of 200 ppm for eye and nose irritation; the LOAEL was 300 ppm. Wirth and Klimmer (1936) reported that slight mucous membrane irritation started to take place in volunteers at exposure concentrations about 278 ppm for a few minutes (unspecified) and that at 1,390 ppm for several minutes, the subjects described prickling in the nose and scratchiness and dryness in the throat. Fairley et al. (1934) reported a NOAEL of 2,000 ppm (only level tested) for respiratory and ocular effects in six subjects exposed to 1,4-dioxane for only 3 minutes. Finally, Yant et al. (1930) described slight eye, nose, and throat irritation in a group of five subjects exposed to 1,600 ppm (only level tested) 1,4-dioxane for only 10 minutes. The available studies in animals used exposure concentrations much higher than the one tested by Young et al. (1977) that often caused death among the animals.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 20
Species: rat

Minimal Risk Level: 1 [ ] mg/kg/day [X] ppm

Reference: Torkelson R, Leong BKJ, Kociba RJ, et al. 1974. 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. Toxicol Appl Pharmacol 30:287-298.

Although there were no adequate intermediate-duration inhalation studies in humans or animals from which to derive an intermediate-duration inhalation MRL, the chronic-duration inhalation MRL of 1 ppm was adopted also for intermediate-duration exposure. The intermediate-duration database for 1,4-dioxane consists of one early study that reports the effects of 1,4-dioxane in several animal species exposed to high doses (lethal in some cases) of 1,4-dioxane (Fairley et al. 1934). Rats, mice, guinea pigs, and rabbits were exposed 3 hours/day, 5 days/week for periods of up to 12 weeks. At termination, examination of the animals revealed moderate to severe liver and kidney toxicity occurring at all exposure levels in all of the species tested. The lowest exposure level was 1,000 ppm.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 20
Species: rat

Minimal Risk Level: 1 [ ] mg/kg/day [X] ppm

Reference: Torkelson R, Leong BKJ, Kociba RJ, et al. 1974. 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. Toxicol Appl Pharmacol 30:287-298.

Experimental design: The chronic-duration inhalation MRL is based on a NOAEL of 111 ppm for liver effects in rats and application of the physiologically-based pharmacokinetic (PBPK) model of Reitz et al. (1990). Source code and parameter values for running the rat and human models in Advance Continuous Simulation Language (ACSL) were provided by Dr. Richard Reitz. A detailed description of the model and its application is presented in Appendix B. In the Torkelson et al. (1974) study, groups of Wistar rats (288/sex) were exposed to 1,4-dioxane vapors at a concentration of 0.4 mg/L (111 ppm) 7 hours/day, 5 days/week for 2 years. Controls were exposed to filtered room air. End points examined included clinical signs, eye and nasal irritation, skin condition, respiratory distress, and tumor formation. Hematological parameters (hemoglobin, red blood cell count, total and differential leukocyte counts, corpuscular volume) were determined after 16 and 23 months of exposure. Blood collected at termination was used also for determination of clinical chemistry parameters (serum ALT and alkaline phosphatase activity, BUN, total protein). Liver, kidneys, and spleen were weighed and the major tissues and organs were processed for microscopic examination.

Effects noted in study and corresponding doses: Exposure to 1,4-dioxane vapors had no significant effect on mortality, or body weight gain and induced no signs of eye or nasal irritation or respiratory distress. Slight but statistically significant changes in hematological and clinical chemistry parameters were within the normal physiological limits and were considered of no toxicological importance. Organ weights were not significantly affected. Microscopic examination of organs and tissues did not reveal treatment-related effects. It should be noted that because no significant effects were seen at the concentration tested, the true study NOAEL is probably higher than 111 ppm. Using the Reitz et al. (1990) model for interspecies extrapolation of 1,4-dioxane dosimetry for data from the Torkelson et al. (1974) study yields a human equivalent NOAEL of 35.5 ppm. Applying an uncertainty factor of 30 (3 for using dosimetric adjustments and 10 for sensitive populations) yields a chronic-duration inhalation MRL of 1 ppm. Using EPA's standard methodology for extrarespiratory effects for a category 3 gas rather than the PBPK model, and an uncertainty factor of 30, results in an MRL of 2 ppm for 1,4-dioxane. The derivation using the PBPK model is preferred because it yields a more protective MRL.

Dose and end point used for MRL derivation: 111 ppm; NOAEL for liver effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] for use of a LOAEL
[X] 3 for extrapolation from animals to humans using dosimetric adjustments
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? NA

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: The exposure concentration was not duration-adjusted.

Other additional studies or pertinent information which lend support to this MRL: The limited human data support the chronic-duration inhalation MRL. An occupational study by Thiess et al. (1976) provided no evidence of ill effects in a group of 74 German workers exposed to concentrations ranging from 0.006 to 14.3 ppm for an average of 25 years. In another epidemiological study, mortality rates were evaluated among workers exposed to 0.1–17 ppm 1,4-dioxane for up to 21 years (Buffler et al. 1978). No differences were found between observed and expected incidences of cancer.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 11
Species: rat

Minimal Risk Level: 4 [X] mg/kg/day [ ] ppm

Reference: JBRC. 1998a. Two-week studies of 1,4-dioxane in F344 and BDF1 mice (drinking water studies). Kanagawa, Japan: Japan Bioassay Research Center.

Experimental design: The acute-duration oral MRL is based on a NOAEL of 370 mg 1,4-dioxane/kg/day for nasal effects in rats. In that study, F344/DuCrj rats (10/sex/group) were administered 1,4-dioxane in the drinking water in concentrations of 0, 1,110, 3,330, 10,000, 30,000, or 90,000 ppm for 2 weeks (0, 130, 370, 1,010, or 2,960 mg/kg/day for males; 0, 160, 400, 1,040, or 2,750 mg/kg/day for females). End points evaluated included clinical signs, food and water consumption, body weight, gross necropsy and histopathology on 2–4 animals per group.

Effects noted in study and corresponding doses: All animals in the 90,000 ppm group died. Two females in the 30,000 ppm (2,750 mg/kg/day) died. Body weight gain was reduced by about 25% in males and females from the 30,000 ppm groups (2,960 mg/kg/day for males, 2,750 mg/kg/day for females). Food and water consumption was reduced approximately by 30% in males and females from the 30,000 ppm group. At 30,000 ppm (2,960 mg/kg/day for males; 2,750 mg/kg/day for females), there was nuclear enlargement of the olfactory epithelium, swelling and vacuolar changes of the central area in the liver, hydropic change of the proximal renal tubule, and vacuolar changes in the brain. At 10,000 ppm, there was nuclear enlargement of the olfactory epithelium (1,010 mg/kg/day in males; 1,040 mg/kg/day in females). The study NOAEL was 400 mg/kg/day in females and 370 mg/kg/day in males (3,330 ppm). Therefore, the dose level of 370 mg/kg/day in male rats is used as the basis for the MRL. The MRL was calculated by dividing the male NOAEL of 370 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for sensitive populations). It should be pointed out that the study has several limitations, including the lack of statistical analysis of the results, only a small number (2–3) of animals were examined, and end points such as hematology, clinical chemistry, clinical signs, and gross examinations were not conducted or reported. Although these limitations compromise the study, the findings are consistent with what is known about target organs for 1,4-dioxane.

Dose and end point used for MRL derivation: 370 mg/kg/day; NOAEL for nasal effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? The conversion was done by the investigators, and the doses listed are means of ranges provided by the investigators.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information which lend support to this MRL: JBRC (1998a) conducted a similar study in male and female Crj:BDF_1 mice and identified NOAELs of 1,380 and 1,780 mg/kg/day for liver effects in males and females, respectively. Doses of 2,550 and 3,220 mg/kg/day caused swelling of the central area of the liver in males and females, respectively. No nasal effects were observed in the mice. Most of the rest of the acute database consists of high-dose early studies aimed at determining LD_{50} values (de Navasquez 1935; Kesten et al. 1939; Laug et al. 1939; Pozzani et al. 1959; Smyth et al. 1941). The lowest dose that caused lethality was 327 mg 1,4-dioxane/kg/day in a study that tested only three dogs (Schrenk and Yant 1936). This dose was provided in the drinking water and killed one dog after 10 days of treatment. Doses of 375 mg/kg/day killed another dog in 9 days. However, because the dogs were allowed to drink the 1,4-dioxane solution only twice daily during a limited period of time, dehydration may have played a role in their death. A gestational exposure study in rats identified a maternal and developmental NOAEL and LOAEL of 513 and 1,033 mg/kg/day, respectively (Giavini et al. 1985).

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 22
Species: rat

Minimal Risk Level: 0.6 [X] mg/kg/day [ ] ppm

Reference: JBRC. 1998b. Thirteen-week studies of 1,4-dioxane in F344 and BDF1 mice (drinking water studies). Kanagawa, Japan: Japan Bioassay Research Center.

Experimental design: The intermediate-duration oral MRL is based on a NOAEL of 60 mg 1,4-dioxane/kg/day for nasal and liver effects in rats. In that study, groups of F344/DuCrj rats (10/sex/group) were administered 1,4-dioxane in the drinking water in concentrations of 0, 640, 1,600, 4,000, 10,000, or 25,000 ppm for 13 weeks (0, 60, 150, 330, 760, or 1,900 mg/kg/day in males; 0, 100, 200, 430, 870, 2,020 mg/kg/day in females). End points evaluated included clinical signs, food and water consumption, body weight, complete hematology and clinical chemistry tests, urinalysis, organ weights, gross necropsy and histopathology. No information was provided as to when the blood and urine samples were collected.

Effects noted in study and corresponding doses: One female in the 25,000 ppm (2,010 mg/kg/day) died. Body weight gain was reduced at 870 and 2,020 mg/kg/day in females and 1,900 mg/kg/day in males. Food consumption was reduced 13% in females at 2,020 mg/kg/day. Water consumption was reduced in a dose-related manner in all male groups and in females at ≥200 mg/kg/day. Hematology test showed significant increases in erythrocyte counts, hemoglobin, hematocrit, and neutrophils, and a decrease in lymphocytes in males at 1,900 mg/kg/day, and decreases in mean corpuscular volume and platelets in females at 2,020 mg/kg/day. Total protein and albumin were decreased in males at ≥330 mg/kg/day and in females at ≥430 mg/kg/day. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), and leucine aminopeptidase (LAP) activities, and levels of cholesterol, triglycerides, sodium, and glucose were significantly elevated in high dose males and females. Urinary pH was decreased in males at ≥330 mg/kg/day and in females at ≥870 mg/kg/day. Absolute and relative kidney weights were increased in females at ≥200 mg/kg/day. Nuclear enlargement of the respiratory epithelium occurred in males at ≥150 mg/kg/day and in females at ≥200 mg/kg/day; nuclear enlargement of the olfactory and tracheal epithelium occurred in males at ≥330 mg/kg/day and in females at ≥430 mg/kg/day. Swelling of the central area of the liver was observed in males at ≥150 mg/kg/day and in females at ≥870 mg/kg/day, and vacuolar changes in the liver occurred in males at ≥760 mg/kg/day and in females at 2,020 mg/kg/day. Nuclear enlargement of the proximal tubule of the kidneys was seen in males at ≥760 mg/kg/day and in females at ≥870 mg/kg/day. Hydropic changes in the proximal tubule of the kidneys and vacuolar changes in the brain occurred in high-dose males and females (1,900 and 2,020 mg/kg/day, respectively). The study LOAEL was 150 mg/kg/day for liver and nasal effects in male rats. To derive the MRL, the NOAEL of 60 mg/kg/day for liver effects in males was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for sensitive populations), yielding an intermediate-duration oral MRL of 0.6 mg/kg/day. Limitations of the study include lack of reporting on clinical signs and gross necropsy.

Dose and end point used for MRL derivation: 60 mg/k/day; NOAEL for liver effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? The conversion was done by the investigators, and the doses listed are means of ranges provided by the investigators.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information which lend support to this MRL: A study by Lundberg et al. 1987) supports the liver findings of JBRC (1998b). The study used male Sprague-Dawley rats (8–11/group) that were treated with 100 or 1,000 mg 1,4-dioxane/kg by gavage in saline 5 days/week for 7 weeks. One week after the last treatment, the rats were killed and the livers were processed for microscopic examination. The livers of high-dose rats showed enlarged foamy hepatocytes mainly in midzonal regions. The foamy appearance was due to vacuoles shown to contain fat. No treatment-related histopathological alterations were observed in the liver at the 100 mg/kg/day dose level.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 39
Species: rat

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] ppm

Reference: Kociba RJ, McCollister SB, Park C, et al. 1974. 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. Toxicol Appl Pharmacol 30:275-286.

Experimental design: Groups of Sherman rats (60/sex/dose level) were treated with 1,4-dioxane in the drinking water at levels of 0 (controls), 0.01, 0.1, or 1% for 716 days. Based on body weight and water consumption data, the investigators estimated that the water provided doses of 1,4-dioxane of 0, 9.6, 94, and 1,015 mg/kg/day for males and 0, 19, 148, and 1,599 mg/kg/day for females. Blood samples were collected from controls and high-dose rats during the 4th, 6th, 12th, and 18th months of the study and at termination. Additional end points evaluated included clinical signs, body weight, organ weights, and gross and microscopic examination of major tissues and organs.

Effects noted in study and corresponding doses: Treatment with 1,4-dioxane significantly increased mortality in high-dose males and females beginning at about 2–4 months of treatment. These rats showed degenerative changes in both the liver and kidneys. Body weight gain was significantly reduced in high-dose animals from the beginning of the study. Microscopic lesions were restricted to the liver and kidneys from the mid- and high-dose groups. The liver lesions consisted of various degrees of hepatocellular degeneration and necrosis and evidence of hepatic regeneration as indicated by hepatocellular hyperplastic nodule formation. The NOAEL for liver effects was 9.6 mg/kg/day in males and 19 mg/kg/day in females. The LOAELs were 94 mg/kg/day in males and 148 mg/kg/day in females. The kidneys showed tubular epithelial degeneration and necrosis, and there was evidence of renal tubular regeneration as indicated by increased tubular epithelial regenerative activity. There were no compound-related alterations in hematological parameters at any time point. The MRL of 0.1 mg/kg/day was calculated by dividing the male rat NOAEL of 9.6 mg/kg/day by an uncertainty factor of 100 (10 to protect sensitive populations and 10 for animal to human extrapolation). The carcinogenic effects were limited to the liver and nasal turbinates from high-dose animals.

Dose and end point used for MRL derivation: 9.6 mg/k/day; NOAEL for liver effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? A conversion was done by the investigators.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information which lend support to this MRL: The NOAEL and LOAEL for liver effects from Kociba et al. (1974) are supported by the results of JBRC (1998c). In that study, groups of Fischer 344/DuCrj rats (50/sex/dose level) received 1,4-dioxane in the drinking water for 104 weeks. 1,4-Dioxane was administered at levels of 0, 200, 1,000, and 5,000 ppm for 2 years (0, 16, 81, and 398 mg/kg/day for males; 0, 21, 103, and 514 mg/kg/day for females). End points evaluated included clinical signs, food and water consumption, body and organ weights, comprehensive hematology and clinical chemistry tests, urinalysis, and gross and microscopic examination of major organs and tissues. In males, relative liver weight was increased at ≥81 mg/kg/day and absolute liver weight was increased at 398 mg/kg/day. A significant increase incidence of spongiosis, hyperplasia, and clear and mixed cell foci was observed in the liver from male rats with ≥81 mg 1,4-dioxane/kg/day, but not 16 mg/kg/day. These lesions were observed in females dosed with 514 mg/kg/day, but not with lower doses. In addition, in this study, female rats dosed with ≥103 mg 1,4-dioxane/kg/day showed nuclear enlargement of the olfactory epithelium of the nasal cavity; no such lesions occurred with the lower female rat dose of 21 mg/kg/day.

The NCI (1978) bioassay in Osborne-Mendel rats used somewhat higher dose levels than Kociba et al. (1974) and JBRC (1998c), but did not observe liver lesions in male rats dosed with 240 mg 1,4-dioxane/kg/day, a dose level that caused liver hyperplasia in male Fischer 344 rats dosed with 81 mg/kg/day or that caused hepatocyte degeneration in Sherman rats dosed with 94 mg/kg/day. Since the dosing method was the same in the three studies, the drinking water, the different results may reflect differences in strain sensitivity.

An alternate approach to derive a chronic-duration oral MRL is to use the PBPK model developed by Reitz et al. (1990), as was done for the chronic inhalation data. Using the model, it can be estimated that the human equivalent dose to the NOAEL of 9.6 mg/kg/day for liver effects in males is 12.9 mg/kg/day. Applying an uncertainty factor of 30 (3 for using dosimetric adjustments and 10 for sensitive populations) to the human NOAEL of 12.9 mg/kg/day yields a chronic-duration oral MRL of 0.4 mg/kg/day, which supports the MRL of 0.1 mg/kg/day derived above. A detailed explanation of the use of the model is presented in Appendix B.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX B. USE OF PBPK MODEL FOR INTERSPECIES EXTRAPOLATION OF 1,4-DIOXANE DOSIMETRY

Interspecies extrapolation (rat-to-human) of 1,4-dioxane dosimetry was achieved using PBPK models described in Reitz et al. (1990). Source code and parameter values for running the rat and human models in Advance Continuous Simulation Language (ACSL) were provided by Dr. Richard Reitz. Parameter values used in the interspecies extrapolation are presented in Table B-1. Accuracy of the implementation of the model in ACSL (v. 11.8.4) was checked against observations reported in Reitz et al. (1990) (results shown in Figures B-1 and B-2).

Two internal dose metrics (DM) were simulated:

(1) The time-integrated 1,4-dioxane concentration in liver (DM1):

$$DM1 = AUCL = \left(\int_0^t \frac{dAL}{dt} \right) \cdot \frac{1}{VL}$$

where AUCL is area under1,4-dioxane liver concentration-time, AL is the amount (mg) of 1,4-dioxane in liver, and VL is the volume of the liver (L).

(2) Daily average time-integrated 1,4-dioxane concentration in liver (DM2):

$$DM2 = \frac{\Sigma AUCL_{i...n}}{N_d}$$

where $AUCL_i$ is the area under the concentration time curve for a single day (24 hoursrs) and N_d is the number of days in the simulation.

Note that DM2 is the time-averaged value of DM1, with an averaging time of 24 hours. The steady-state value of DM2 fluctuates (periodically) during an intermittent exposure (i.e., 7 hours/day, 5 days/week), whereas the value of DM1 increases over time, with the *rate of increase* fluctuating periodically, once a steady state is reached. If the simulated exposure duration is held constant, both DM1 and DM2 produce nearly identical inter-species external dose extrapolations. This was confirmed in the current analysis. Although DM2 was reported in Reitz et al. (1990), the results reported here are for DM1 (Table B-2), which can be more readily duplicated for a given exact exposure duration (i.e., there is no periodicity in DM1).

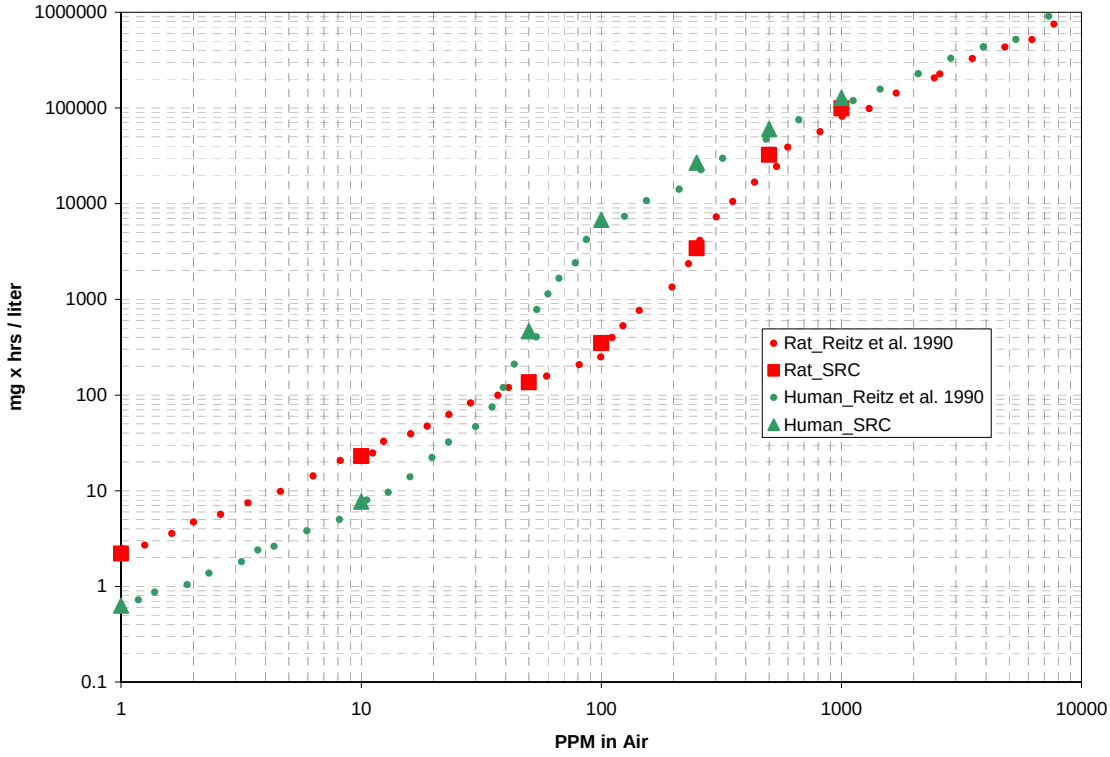
Exposures in the Torkelson et al. (1974) rat inhalation study were simulated as exposures of a 0.4-kg rat to 111 ppm (400 mg/m^3), 7 hours/day (7 hours/24 hours), 5 days/week (120 hours/168 hours) for 2 years (17,420 hours). The predicted value for DM1 corresponding to this exposure was 53,079 mg-hour/L (row 1 of Table B-2). Human equivalent exposure concentrations (HEC) were simulated as exposures of a 70-kg human for 24 hours/day, 7 days/week for 2 years. The human model was run iteratively, varying the external exposure concentration until the model converged on the value for DM1 for the rat. The HEC that corresponded to a value of DM1 of 53,079 mg-hour/L was 35.5 ppm (128 mg/m^3, row 2, Table B-2).

Table B-1. Parameters Values for Rat and Human 1,4-Dioxane Models[a]

Parameter	Definition	Rat model	Human model
BW	Body weight (kg)	0.4	70
VLC	Liver volume (fraction of body)	0.04	0.031
VFC	Fat volume (fraction of body)	0.05	0.231
VSC	Rapidly-perfused tissue volume (fraction of body)	0.05	0.037
VRC	Slowly-perfused tissue volume (fraction of body)	0.70	0.561
VB	Blood volume (fraction of body)	0.05	0.05
QCC	Cardiac output (L/hour-kg body weight)	15.0	30.0
QPC	Alveolar ventilation rate (L/hour-kg body weight)	15.0	30.0
QLC	Liver blood flow (fraction of cardiac output)	0.25	0.25
QFC	Fat blood flow (fraction of cardiac output)	0.05	0.05
QSC	Rapidly-perfused blood flow (fraction of cardiac output)	0.52	0.52
QRC	Slowly-perfused blood flow (fraction of cardiac output)	0.18	0.18
PB	Blood:air partition coefficient	1,850	3,660
PL	Liver:air partition coefficient	1,557	1,557
PF	Fat:air partition coefficient	851	851
PS	Rapidly-perfused:air partition coefficient	1,557	1,557
PR	Slowly-perfused:air partition coefficient	1,557	1,557
VMAXC	Maximum rate of metabolism (mg/hour-kg body weight)	13.7	6.35
KM	Michaelis-Menten coefficient for metabolism (mg/L)	29.4	3.0
KA	Rate constant for gastrointestinal absorption ($hour^{-1}$)	5.0	5.0
KME	Rate constant for elimination of metabolites ($hour^{-1}$)	0.28	0.56

[a]Reitz et al. (1990)

Figure B-1. Comparison of Model Output Reported in Reitz et al. (1990, Figure 5a) and from SRC Version of the Reitz et al. (1990) 1,4-Dioxane Model (Inhalation)

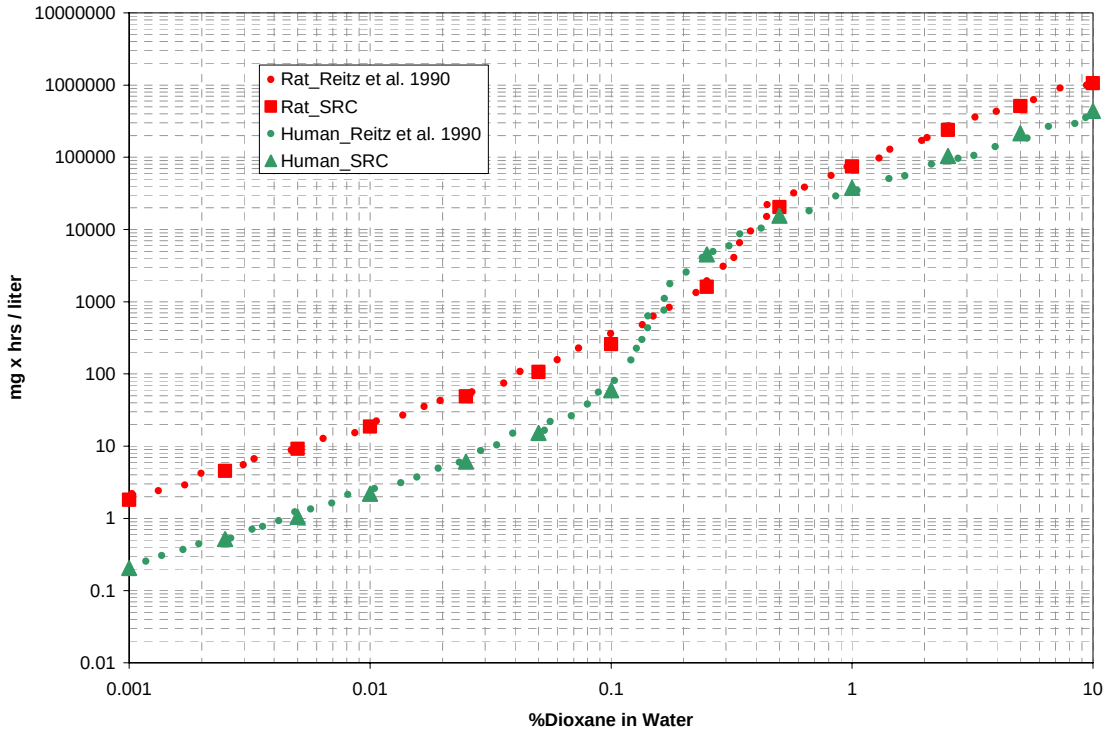


Simulations are of the average daily area under concentration–time curve for 1,4-dioxane in liver, for a 2-year (17,520 hours) continuous inhalation exposure (AAUCL, mg-hours/L)

$$AAUCL = \frac{\Sigma AUCL_{i...n}}{N_d}$$

where $AUCL_i$ is the area under the concentration time curve for a single day (24 hours) and N_d is the number of days in the simulation. Simulations are of a 0.4-kg rat and 70-kg human.

Figure B-2. Comparison of Model Output Reported in Reitz et al. (1990, Figure 5a) and from SRC Version of the Reitz et al. (1990) 1,4-Dioxane Model (Oral)



Simulations are of the average daily area under concentration–time curve for 1,4-dioxane in liver, for a 2-year (17,520 hours) continuous exposure to 1,4-dioxane in drinking water (AAUCL, mg-hours/L)

$$AAUCL = \frac{\Sigma AUCL_{i...n}}{N_d}$$

where $AUCL_i$ is the area under the concentration time curve for a single day (24 hours) and N_d is the number of days in the simulation. Simulations are of a 0.4-kg rat and 70-kg human; water consumption IR_{water} was assumed to be 0.054 L/day in the rat and 2 L/day in the human:

$$IR_{water} = 0.102 \cdot BW^{0.7}$$

Table B-2. Summary of Internal Dose Predictions and Corresponding Human and Rat Equivalent Doses for Rat Inhalation Study

Species	Strain	Gender	BW (kg)	Route	ED (yr)	EF1 (day/wk)	EF2 (hr/day)	EC (ppm)	EC (mg/m^3)	DM1 (mg hr/L)	HDM/ RDM
Rat	-	male	0.4	I	2	5	7	111.0	400	53079	-
Human	-	-	70	I	2	7	24	35.5	128	53081	0.32

BW=body weight; DM=dose metric; EC exposure concentration; ED=exposure duration, EF=exposure frequency; HDM=human dose metric; hr=hour; kg-kilogram; L=liter; mg=milligram; ppm=parts per million; RDM=rat dose metric; wk=week; yr=year

Exposures in the Kociba et al. (1974) rat drinking water study were simulated as exposures of a 0.4-kg rat to 9.6 mg/kg/day, 24 hours/day, 7 days/week for 2 years. The predicted value for DM1 corresponding to this exposure was 9,610 mg-hour/L (row 1 of Table B-3). Human equivalent doses (HED) were simulated as exposures of a 70 kg human for 24 hours/day, 7 days/week for 2 years (drinking water intake, 2 L/day). The HED that corresponded to a value of DM1 of 9,620 mg-hour/L was 12.9 mg/kg-day (row 2, Table B-3). In the above simulations, both the rat and human drinking water exposures were assumed to be distributed uniformly over a 24-hour period. However, simulations were also run, assuming distribution of the exposure over a 12-hour period (i.e., awake hours when water would be consumed); the value for the HED was 19% lower when a 12-hour/day exposure frequency was assumed (10.5 mg/kg/day) compared to the value obtained when a 24-hour/day exposure frequency was assumed (12.9 mg/kg/day).

Uncertainties in Use of a PBPK Model for Interspecies Extrapolation of 1,4-Dioxane Dosimetry in the inhalation modeling..

The predicted slope of the relationship between exposure concentration and DM1 (and DM2), in humans, is extremely steep in the range of 10–100 ppm; the range in which the dose-equivalence calculations were made for the rat inhalation study (see Figure B-1). Over this range, a 10-fold change in exposure concentration corresponds to a 900-fold change in the dose metric. By contrast, the corresponding change predicted by the rat model is 15-fold. This difference translates into a much higher sensitivity of the dose metric in humans to small changes in assumed exposure concentration, compared to rats. For example, the value of DM1 for a human exposure concentration 5 ppm above the HEC (40 ppm) is 83,320; a 1.57-fold increase above the value that corresponds to the NOAEL (53,081). We have no basis for determining whether such relatively small increases in exposure concentration (14%), above the $NOAEL_{HEC}$ would or would not have adverse consequences.

Table B-3. Summary of Internal Dose Predictions and Corresponding Human and Rat Equivalent Doses for Rat Drinking Water Study

Species	Strain	Gender	BW (kg)	Route	ED (yr)	EF1 (day/wk)	EF2 (hr/day)	EC (ppm)	Dose (mg/kg/day)	DM1 (mg hr/L)	HDM/ RDM
Rat	-	male	0.4	W	2	7	24	100	9.6	9611	-
Human	-	-	70	W	2	7	24	452	12.9	9611	1.35

BW=body weight; DM=dose metric; EC=exposure concentration; ED=exposure duration; EF=exposure frequency; HDM=human dose metric; hr=hour; kg=kilogram; L=liter; mg=milligram; ppm=parts per million; RDM=rat dose metric; wk=week; yr=year

APPENDIX C. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page C-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered

in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page C-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the

extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

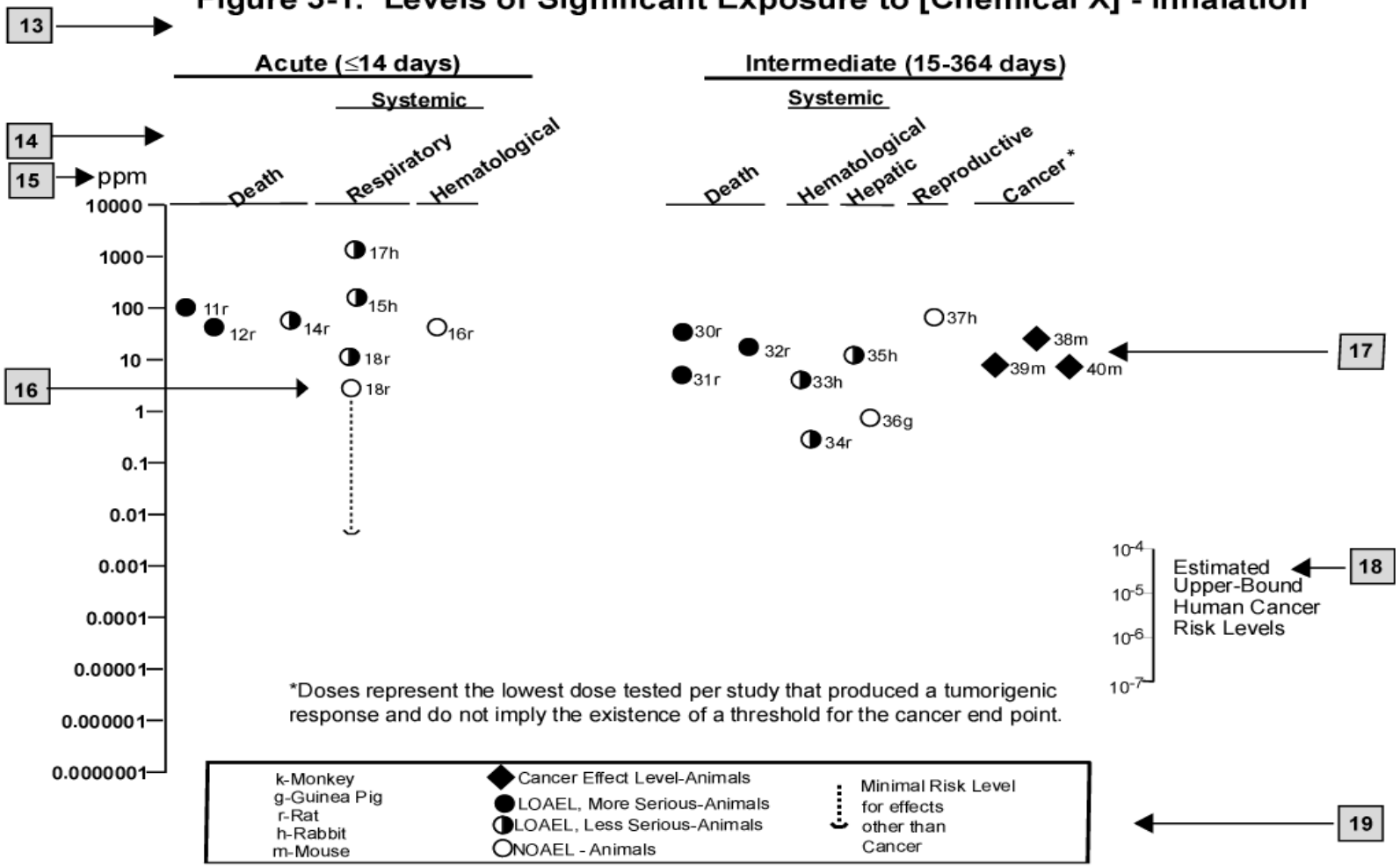
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX D. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX E. INDEX